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Original Research

Peripheral stem cell mobilization strategies in patients with autologous hematopoietic cell transplantation: A single center's experience

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HIGHLIGHTS

The white blood cell count was inversely correlated with the success of mobilization

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A B S T R A C T

This research is to investigate the parameters which may affect the mobilization of stem cells in patients receiving autologous hematopoietic peripheral blood stem cell transplantation (PBSCT). A retrospective study was carried out using the data derived from the medical files of 242 patients who received PBSCT. Descriptive, clinical, and laboratory parameters were compared between patients with successful and unsuccessful stem cell mobilization. Successful stem cell mobilization ratio was 4.463 times higher when preemptive plerixafor was administrated; 1.032 times higher when CD34+ cell count increased 1 unit at the beginning of mobilization. The white blood cell count was inversely correlated with the success of mobilization. An increase of 1 unit in WBC count was associated with a 1.027 times decrease in the success rate. The data indicated that the administration of preemptive plerixafor and CD34+ cell count at the beginning of mobilization were directly related to the success of mobilization after PBSCT. On contrary, WBC count was inversely associated with the success rate.

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1. INTRODUCTION

High dose chemotherapy and bone marrow transplantation are common therapeutic modalities used in the management of hematological malignancies. An adequate number and

quality of stem cells must be infused to achieve a favorable autologous bone marrow transplantation. Relevant studies indicated that infusion of minimally $2x10^6$ cells/kg of CD34+ stem cells is enough for a satisfactory neutrophil and platelet engraftment on the 14th day following the transplantation.[1] Mobilization is defined as the removal of the hematopoietic progenitor cells (HPCs) from the bone marrow to the peripheral blood.[2]

Autologous transplantations and most allogeneic transplantations are currently performed primarily with peripheral blood stem cells (PBSCs) rather than stem cells from the BM. Because it is associated with high rates of cell collection, quicker engraftment diminished possibility of complications, simpler accessibility, lesser rates of tumor contagion, and quicker hematopoietic and immune restructuring.[3] Since successful hematopoietic peripheral blood stem cell transplantation (PBSCT) is associated with the quality and number of infused stem cells, the factors that may influence stem cell mobilization have been primarily studied.[3] It has been reported that the diagnosis of the patient, chemotherapy protocols, frequency of relapses, growth factors, and brand of apheresis devices as well as leukocyte and CD34+ cell counts on the 1st day of apheresis may influence the success of mobilization. The discrepancies in the outcomes of studies may be due to the small sample size, the inclusion of various mobilization regimens in the analysis, and the vagueness of the well-established benchmarks for successful mobilization.

The mobilized PBSCs constitute the primary source for hematopoietic PBSCT after myeloablative therapy. The conventional protocols for PBSCs mobilization involve the employment of granulocyte colony-stimulating factor (G-CSF) only or in combination with other myelosuppressive chemotherapeutics.[4] The recognition and elucidation of factors that influence stem cell mobilization are critical in optimizing therapeutic outcomes. Our purpose was to investigate the success of peripheral stem cell mobilization strategies in patients with autologous hematopoietic cell transplantation in our center and variables that may affect the mobilization of stem cells.

2. MATERIAL AND METHOD

Study design

This retrospective study was performed using medical records of 242 patients (158 males, 84 females) treated in the bone marrow transplantation unit of the hematology department of our tertiary care center between 2014 and 2018. The approval of the local Institutional Review Board was obtained before the study. The study has been implemented in adherence to the principles of the Helsinki Declaration.

According to our institutional policy, the initial mobilization attempt was performed with 10 µg/ kg/d G-CSF alone in patients with low tumor burden. Patients who needed salvage chemotherapy received G-CSF (10 µg/kg/d) in combination with chemotherapy. For poor mobilizers in G-CSF alone group, chemotherapy followed by G-CSF was preferred as a second line mobilization regimen. Chemotherapy was either high dose cyclophosphamide or salvage chemotherapies according to the primary disease of the patients.

On the other hand in patients who were mobilized with G-CSF plus chemotherapy enumeration of CD34 + cells in the peripheral blood was assessed when blood leukocyte count exceeds $1000/mm^3$ and apheresis was performed when the peripheral CD34+ cell count was $>20/mm^3$. Total nucleated and CD34+ cell count of the apheresis product was measured with flow cytometry.

Stem cell mobilization was assigned as unsuccessful in 65 (26.9%) patients, and successful in 177 (73.1%) patients according to the criteria defined by Gertz et al.[5] The success of mobilization is classified into three groups with respect to the CD34+ cell count collected after mobilization and leukapheresis: 1) Failure: CD34+ cell count < $1x10^6$/kg; 2) Poor: $1x10^6$/kg ≤ CD34+, cell count < $5x10^6$/kg; 3) Successful: CD34+ cell count ≥ $5x10^6$/kg.[5] In this study, failure and poor mobilization were accepted as unsuccessful, and their descriptive, clinical, and hematological parameters were compared with patients with successful outcomes.

The most common diagnoses were multiple myeloma (n=111; 45.9%), non-Hodgkin lymphoma (n=70; 28.9%), and Hodgkin's disease (n=43; 17.8%). For stem cell mobilization,

Filgrastim was utilized in many patients (n=231; 95.5%), while lenograstim was used in 11 (4.5%) patients. Accompanying comorbidity was detected in 61 patients (25.2%). Radiotherapy was administered in 24 patients (9.9%). The disease was stage 3 (n=107; 44.2%), stage 4 (n=62; 25.6%), stage 2 (n=23; 9.5%) and stage 1 (n=8; 3.3%).

A single dose of preemptive plerixafor was administered for stem cell mobilization in 28 patients (11.6%). There was refractory thrombocytopenia in 11 cases (4.5%). Leukapheresis has performed in case the CD34+ cell count in circulation was greater than 10/µL, for patients who were treated by chemotherapy and granulocyte colony-stimulating factor (G-CSF). The leukapheresis was performed on the 5th day in patients treated by G-CSF alone.

Statistical analysis

Data were analyzed via the Statistical Package for Social Sciences program version 21.0 (*SPSS Inc., Chicago, IL, USA*). Data are expressed as mean±SD or median (interquartile range), as appropriate. All differences associated with a chance probability of .05 or less were considered statistically significant. The initial evaluation of variables that may influence the success of mobilization was performed with univariate logistic regression analysis. The variables that yielded a p-value <0.020 were determined and involved in multiple logistic regression analysis.

3. RESULTS AND DISCUSSION

In Table 1, the descriptive statistics and univariate logistic regression analysis results for categorical variables are presented. The comparison of groups with successful and unsuccessful stem cell mobilization indicated that there was no statistically significant difference between 2 groups as for sex distribution (p=0.864), disease stage (p=0.946), G-CSF type (filgrastim or lenograstim) (p=0.511), presence of comorbidities (p=0.464), refractory thrombocytopenia (p=0.476) and administration of radiotherapy (p=0.478). A significant relationship between the administration of preemptive plerixafor and success rate was observed.

The administration of preemptive plerixafor increased the success rate by 4.463 times. The comparative analysis of the impacts of various chemotherapy protocols indicated that doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) and gemcitabine, dexamethasone and cisplatin (GDP) (p=0.554); high dose dexamethasone (HIDEX) and Velcade®, cyclophosphamide and dexamethasone (VCD) (p=0.497); and Velcade®, cyclophosphamide and dexamethasone (VCD) alone had no significant effect on the success of mobilization (Table 2).

Table 3 demonstrates the results of the univariate logistic regression analysis for quantitative variables. There was a noteworthy correlation between CD34+ cell count at the beginning of mobilization and the success rate. Every increase in CD34+ cell count was associated with a 1.032 times amplification of the success rate of mobilization.

Multivariate logistic regression analysis was performed on variables with a p-value < 0.020 in univariate logistic regression analysis. The results of multivariate regression analysis are demonstrated in Table 4, and the mobilization success rate is affected by white blood cell (WBC) count and CD34+ cell count at the onset of mobilization. Every increase in WBC count was associated with 1.027 times decrease in the success rate of mobilization. On the other hand, each increase in CD34+ cell count was associated with a 1.037 times increase in the mobilization success rate.

The determination of risk factors linked with the accumulation of peripheral blood stem cells in various malignancies is essential in taking appropriate therapeutic decisions. Recently, some of the confounding and contributory factors have been identified, and efforts have been spent on the development of new mobilization strategies.

These results supported the publication by Jansen et al., which suggested that the CD34+ cell count may have a predictive role in the myeloablative therapy.[6] In contrast to studies supporting that prior radiotherapy may adversely affect mobilization, we did not observe any unwanted impact of radiotherapy.[7,8] In this study, the most unfavorable predictive

factor for progenitor cell output was the intensity of previous chemotherapy.[9,10] Chemotherapy regimens under investigation did not yield any obvious effect on the success rate of stem cell mobilization; however, we had a wide spectrum of chemotherapy protocols, and only 3 of them could be analyzed due to the small number of participants in each subgroup. Pre-emptive plerixafor administration has a remarkable and favorable effect on the success rate of mobilization. Further studies of new mobilization agents and their combination regimens are warranted to evaluate the outcomes of stem cell mobilization and to overcome the failure of mobilization.

The stem cells collected after a sequence of chemotherapy contained notably fewer plasma cells compared to those collected after a single high-dose drug administration. Different strategies were studied in MM patients for HSC harvesting and tandem transplantation.[11,12,13] There was an inverse correlation between CD34+ stem cell counts on the 9th day and neutrophil engraftment. This inverse correlation is noteworthy since it reminded that higher CD34+ stem cell levels by the 9th day, resulted in earlier neutrophil engraftment. Thus, the quantification of CD34+ stem cell levels on the 9th day may yield valuable information for autologous hematopoietic PBSCT.[14,15] Further trials must be implemented to evaluate the validity and significance of this finding.

Factors likely to affect total harvested cells involve >3 cycles of apheresis for an apheresis period, mobilization with lenograstim, harvesting with Fresenius device, and ≥ 35000 WBC counts on the 1st day of apheresis.[16,17,18] Moreover, factors that affect total harvested CD34+ cell count were reported as diagnosis, peripheral blood WBC counts on the 1st day of apheresis, harvesting with Fresenius device, and mobilization with filgrastim. The patient's diagnosis is an important parameter for the achievement of the highest total CD34+ cell counts. The success of the collection of CD34+ cells was highest in Hodgkin's disease and multiple myeloma. On the other hand, the lowest rate was detected in acute leukemias. This difference may arise from the high rate of stem cell damage due to the salvage treatments used in acute leukemia. This negative effect on the CD34+ cell mobilization is consistent with previous studies.[16,17,18] Many studies reported the impact of peripheral blood WBC and CD34+ cell counts on the success of mobilization at first-day apheresis.[16,19,20,21,22]

Our data yielded that gender distribution, disease stage, type of G-CSF type (filgrastim or lenograstim), the presence of comorbidities, refractory thrombocytopenia, and administration of radiotherapy did not influence the success of mobilization. However, the administration of preemptive plerixafor increased the success rate in univariate analysis. In multiple clinical studies, the combination of plerixafor with G-CSF resulted in more significant mobilization in CD34+ cells than G-CSF alone and more successful retrieval of hematopoietic stem cells from donors and better engraftment in recipients.[23] Fergadis et al. stated that plerixafor was useful to mobilize enough numbers of peripheral blood stem cells in relapsed malignancies after previous single or tandem high-dose chemotherapy and PBSCT.[24] Tolomelli et al., evaluated 37 multiple myeloma patients and stated that the timing of plerixafor administration influences immunological recovery.[25] Yang et al., analyzed the effectivity of plerixafor use for successful stem cell mobilization in non-Hodgkin lymphoma and multiple myeloma. Their findings indicated that the additional use of plerixafor to G-CSF provides an increased HSC collection in a shorter duration without any increase in adverse events.[26] Gutiérrez-Aguirre et al. demonstrated that the use of reduced doses of plerixafor might suffice to gather at least 2×10^6 /kg CD34.[27] Yoshifuji et al., stated that the use of plerixafor with an enough washout period may contribute to the successful mobilization after the use of pomalidomide.[28] Danner et al., have addressed the impact of serum albumin on homeostatic hematopoiesis and pharmacological mobilization of hematopoietic stem and progenitor cells.[29] Multivariate analysis indicated that higher counts of CD34+ cell count were associated with better success rates for mobilization, while increased WBC count was associated with the diminished success of mobilization. Although some publications supported that lenograstim was more potent than filgrastim for improvement of the success rate, our data did not confirm this postulate.[30,31] However, there was a remarkable equilibrium between patients receiving filgrastim and lenograstim in our series. Thus, understanding whether filgrastim is more

effective in the mobilization of progenitor cells and the recruitment of mature cells to the peripheral blood cells necessitates further prospective trials on larger series.

These findings yielded that gender, radiotherapy, and comorbidities did not alter the number of harvested CD34+ cells. This finding is controversial to the reports stating that radiotherapy exerted a negative effect on stem cell mobilization.[7,8] The other factors that may affect the success rate of mobilization involved qualitative and quantitative variability of the hematopoietic stem cells in the bone marrow, differences in the migration capacity of hematopoietic stem cells, and decreased response to G-CSF. Our results are consistent with previous reports stating that leukapheresis success was associated with CD34+ cell count in peripheral blood before the intervention.[32]

The factors reported herein may be also important for other cell therapies such as autologous bone marrow-derived mononuclear cells (BMDMC). Morales et al., reported that the instruction of BMDMCs through bronchoscope seems to be a feasible and safe method in accelerated and chronic silicosis.[33] Assmus et al., stated that repeated intra-coronary administration of BMDMCs seems to be linked with improvement of clinical outcomes compared with single treatment at 2 years in patients with heart failure after myocardial infarction.[34]

The main restrictions of this study are retrospective design and data confined to the experience of a single center. Although the patient number analyzed in this study was not few for a single-center study, still those are heterogeneous in many clinical backgrounds and the sample size of each patient group with a similar background is relatively small.

To sum up, these factors must be remembered before stem cell apheresis and more convenient decisions can be made in terms of the preparation procedures, the selection of technical measures, and apheresis devices. These parameters may all contribute to the improvement of the success of mobilization. A better understanding of mechanisms of mobilization will aid in the determination of the optimal time and using synergistic agents to have enough CD34+ cells. This approach will help the accomplishment of a cost-effective modality for hematopoietic stem cell transplantation.

CONCLUSION

To conclude, this research results indicated that the administration of preemptive plerixafor and CD34+ cell count at the beginning of mobilization were directly related to the success of mobilization in hematopoietic stem cell mobilization. On the contrary, WBC count was inversely associated with the success rate. Consideration of these points during the selection of patients and the establishment of the treatment plan may be useful to achieve better treatment outcomes.

DISCLOSURE STATEMENT

The authors declare that they have no conflict of interest.

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Table 1. The comparison of groups with successful and unsuccessful stem cell mobilization for clinical variables (univariate logistic regression analysis)

Variable		Unsuccessful (n=65)	Successful (n=177)	Odds Ratio	Sig.*
Sex	Female	22 (26.2)	62 (73.8)	1.054	0.864
	Male	43 (27.2)	115 (72.8)		
Diagnosis	AML	0 (0.0)	1 (100.0)	1.235	0.160
	HL	11 (25.6)	32 (74.4)		
	MM	26 (23.4)	85 (76.6)		
	NHL	25 (33.7)	49 (66.3)		
	Solid tumor	3 (23.1)	10 (76.9)		
Stage	1	3 (37.5)	5 (62.5)	1.014	0.946
	2	4 (17.4)	19 (82.6)		
	3	34 (31.8)	73 (68.2)		
	4	17 (27.4)	45 (72.6)		
Remission before mobilization	CR	39 (31.0)	87 (69.0)	N/A	N/A
	Chemosensitive	0 (0.0)	2 (100.0)		
	PR	23 (28)	59 (72)		
	Progressive	0 (0.0)	2 (100.0)		
	Refractory	3 (18.8)	13 (81.3)		
	Stable	0 (0.0)	3 (100.0)		
	VGPR	0 (0.0)	10 (100.0)		
Mobilization regimen	G-CSF	36 (28.3)	91 (71.7)	4.285	*0.03*
	G-CSF + CT	13 (14.8)	75 (85.2)	6.923	*0.004*
	G-CSF+ Plerixafor	10 (66.7)	5 (33.3)	3.033	0.81
	CT + G-CSF + Plerixafor	6 (54.5)	5 (45.5)	0.6	0.532
G-CSF type	Filgrastim	63 (27.3)	168 (72.7)	1.687	0.511
	Lenograstim	2 (18.2)	9 (81.8)		
Filgrastam type	Granocyte®	2 (18.2)	9 (81.8)	1.125	0.895
	Leucostim®	30 (32.6)	62 (67.4)	0.517	0.167
	Neuopogen®	26 (25.0)	78 (75.0)	0.75	0.548
	Tevagrastim®	7 (20.0)	28 (80.0)	-	-
Preemptive plerixafor	Yes	16 (57.1)	12 (42.9)	4.463	*<0.001*
	No	49 (23.0)	164 (77.0)		
Co-morbidity	No	45 (24.9)	173 (75.1)	1.295	0.464
	Yes	15 (30.0)	46 (70.0)		
Refractory thrombocytopenia	No	61 (26.5)	169 (73.5)	1.582	0.476
	Yes	4 (36.4)	7 (63.6)		
Radiotherapy	No	57 (26.5)	158 (73.5)	1.385	0.478
	Yes	8 (33.3)	16 (66.7)		

* p value obtained after univariate logistic regression analysis.
CT: chemotherapy; AML: acute myeloid leukemia; HL: Hodgkin lymphoma; NHL: non-Hodgkin lymphoma; MM: multiple myeloma; DLBCL: diffuse large B-cell lymhoma; N/A: not applicable; G-CSF: granulocyte colony stimulating factor; CR: complete remission; PR: partial remission; VGPR: very good partial remission

Table 2. The comparison of groups with successful and unsuccessful stem cell mobilization for the impact of chemoterapy regimens (univariate logistic regression analysis)

Variable	Total number	Unsuccessful	Successful	Odds Ratio	Sig.*
VCD	4	1 (25.0)	3 (75.0)	N/A	N/A
ABVD + GDP	19	4 (21.1)	15 (78.9)	1.412	0.554
ABVD + ICE	6	2 (33.3)	4 (66.7)	N/A	N/A
BEP + TIP	4	0 (0.0)	4 (100.0)	N/A	N/A
CHOP	7	2 (28.6)	5 (71.4)	N/A	N/A
HIDEX + VCD	40	9 (22.5)	31 (77.5)	1.321	0.497
HIDEX + VTD	8	3 (37.5)	5 (62.5)	N/A	N/A
R- CHOP	8	6 (75.0)	2 (25.0)	N/A	N/A
RCHOP + GDP	9	4 (44.4)	5 (55.6)	N/A	N/A
VAD + VCD	13	5 (38.5)	8 (61.5)	N/A	N/A
VTD	27	4 (14.8)	23 (85.2)	2.278	0.143

VIDE	5	2 (40.0)	3 (60.0)	N/A	N/A

VCD: Velcade®, cyclophosphamide and dexamethasone; ABVD: Doxorubicin, bleomycin, vinblastine and dacarbazine; GDP: gemcitabine, dexamthasone and csiplatin; ICE: ifosfamide, carboplatin and etoposide; BEP: bleomycin, etopopsid and platinum; TIP: paclitaxeli ifosfamide and cisplatin; CHOP: cyclophosphamide, doxorubicin, vincristine and prednisolone; HIDEX: high dose dexamethasone; VTD: Velcade®, thalidomide and dexamethasone; VAD: vincristine, doxorubicin and dexamethasone; N/A: not applicable

Table 3. The comparison of groups with successful and unsuccessful stem cell mobilization for hematologic parameters (univariate logistic regression analysis)

Variable	Unsuccessful (n=65)	Successful (n=177)	Odds Ratio	Sig.*
Age	52.25± 14.95 55 [17 - 75]	49.58± 14.051 53 [14 - 75]	1.013	0.199
No. of cures before mobilization	7.51 ± 3.37 6 [3 - 19]	6.80 ± 3.37 6 [2 - 34]	1.059	0.162
No. of sequences before mobilization	1.91 ± 0.99 2 [1 - 6]	1.86 ± 0.70 2 [1 - 4]	1.072	0.701
No. of mobilization procedures	2.12 ± 0.72 2 [1 – 4]	1.92 ± 0.85 2 [1 – 4]	1.351	0.089
White blood cell count before mobilization	32.60± 20.64 35.41 [2.14 – 85.8]	27.05± 20.08 22.8 [1.52 – 69.67]	1.013	0.061
Haemoglobin level before mobilization	11.86 ± 2.03 12.1 [6.96 – 16.1]	11.49 ± 1.99 11.7 [0 – 15.5]	1.102	0.202
Platelet count before mobilization	158.63 ± 87.77 155 [12 - 366]	149.57± 95.60 139 [6 - 418]	1.00	0.503
Peripheral CD34+ count in the beginning of mobilization	30.57± 28.34 23.13 [0 – 208.82]	73.43± 80.20 40.28 [0478.86]	1.032	*<0.001*
The duration of mobilization	7.34 ± 5.85 4 [3 - 33]	8.65 ± 5.89 5 [1 - 39]	1.042	0.131

* p value obtained after univariate logistic regression analysis.

Table 4. Multivariate logistic regression analysis of the variables with statistical difference in univariate logistic regression analysis

	B-value	SE	Wald	Odds Ratio	95% CI	Significance
Preemptive plerixafor administration	-0.561	0.474	1.401	0.1752	0.692 – 4.434	0.237
No. of cure(s)	-0.020	0.047	0.182	0.980	0.893 – 1.075	0.670
Sequences of mobilization	0.296	0.231	1.646	1.344	0.855 – 2.112	0.199
White blood cell count	-0.026	0.009	8.235	0.974	0.957 – 0.992	*0.012*
CD34+ cell count in the initiation of mobilization	-0.737	0.008	18.624	1.037	1.020 – 1.054	*<0.001*